NIDN-10439

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	I. Henriksen, et al.	Group Art Unit:	To be assigned
Serial Number:	To be assigned	Examiner:	To be assigned
Filing Date:	February 8, 2002		
Title:	Administering a Gravity Segregation Dispersion by Continuous Infusion		

FIRST PRELIMINARY AMENDMENT

Honorable Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a continuation of international application number PCT/GB00/03310 filed August 25, 2000. This application also claims priority to application number 9920392.9 filed August 27, 1999 in Great Britain. Additionally, this application claims the benefit of United States provisional application number 60/153,018 filed September 9, 1999.

In the Specification

Please amend page 1, line 4, by inserting the following sentence and heading:

-- This application is a continuation application of international application number PCT/GB00/03310 filed August 25, 2000, the entire disclosure of which is hereby incorporated by reference.

Background of Invention--

Please amend page 3, line 24, by inserting the following heading:

--Summary of Invention--

Please amend page 4, line 28, by inserting the following paragraph and headings:

--Brief Description of the Figures

In the accompanying figures:

Fig. 1 is a schematic representation of one embodiment of apparatus useful in accordance with the invention;

Fig. 2 comprises plots of microbubble concentration against infusion time for the *in vitro* test system described in Example 6 hereinafter and for a comparative study using a horizontally positioned syringe; and

Fig. 3 comprises plots of echogenicity against time obtained in accordance with the *in vivo* studies described in Example 15 hereinafter.

Referring to Fig. 1 in more detail, syringe driver 1 (detail not shown) is adapted to receive vertically positioned syringe 2 and controllably to drive syringe plunger 3 in an upward direction so as to expel dispersion 4 through delivery outlet 5 at the upper extremity of the syringe. Three way stopcock 6 connects outlet 5 and feed 7 from saline infusion minibag 8 to conduit tube 9 which is connected *via* Luer lock 10 to infusion feed line 11, which in turn is connectable to an injection needle or catheter (not shown). The flow rate of dispersion is controllable by adjusting syringe driver 1. The flow rate of

saline from minibag 8 is controllable by adjusting one or more of stopcock 6, valve 12 and the height of the minibag.

The following non-limitative examples serve to illustrate the invention.

Detailed Description of the Invention--

Please amend page 12, lines 1-27, by deleting the following:

[In the accompanying drawings:

Fig. 1 is a schematic representation of one embodiment of apparatus useful in accordance with the invention;

Fig. 2 comprises plots of microbubble concentration against infusion time for the *in vitro* test system described in Example 6 hereinafter and for a comparative study using a horizontally positioned syringe; and

Fig. 3 comprises plots of echogenicity against time obtained in accordance with the *in vivo* studies described in Example 15 hereinafter.

Referring to Fig. 1 in more detail, syringe driver 1 (detail not shown) is adapted to receive vertically positioned syringe 2 and controllably to drive syringe plunger 3 in an upward direction so as to expel dispersion 4 through delivery outlet 5 at the upper extremity of the syringe. Three way stopcock 6 connects outlet 5 and feed 7 from saline infusion minibag 8 to conduit tube 9 which is connected *via* Luer lock 10 to infusion feed line 11, which in turn is connectable to an injection needle or catheter (not shown). The flow rate of dispersion is controllable by adjusting syringe driver 1. The flow rate of

saline from minibag 8 is controllable by adjusting one or more of stopcock 6, valve 12 and the height of the minibag.

The following non-limitative examples serve to illustrate the invention.]

Please amend page 13, line 1, by inserting the following heading and paragraph:

--Examples

The following examples illustrate certain preferred embodiments of the instant invention but are not intended to be illustrative of all embodiments.--

Please amend page 16, line 21, by inserting the following paragraph:

-- It is apparent that many modifications and variations of the invention as hereinabove set forth may be made without departing from the spirit and scope thereof. The specific embodiments described are given by way of example only, and the invention is limited only by the terms of the appended claims.--

In the Claims

Please amend page 17, line 1, as follows:

[**Claims**]What is claimed is:

Please cancel claim 18, without prejudice.

Please amend claim 1 as follows:

1. (once amended) [A]In a method of administering a gravity segregating dispersion to a subject by continuous infusion, [wherein said dispersion is controllably delivered]the improvement comprising controllably delivering said dispersion from an upper or lower extremity of an essentially vertically positioned delivery vessel and thereafter [is admixed]admixing with a flushing medium prior to administration to the subject.

Please amend claim 2 as follows:

2. (once amended) [A]The method [as claimed in]of claim 1 wherein said delivery vessel comprises a syringe.

Please amend claim 3 as follows:

3. (once amended) [A]The method [as claimed in]of claim 2 wherein delivery of said dispersion from said syringe is controlled by a syringe driver.

Please amend claim 4 as follows:

4. (once amended) [A]The method [as claimed in any of the preceding claims]of claim 1 wherein said dispersion is a gas-containing contrast agent.

Please amend claim 5 as follows:

5. (once amended) [A]The method [as claimed in]of claim 4 wherein said gas comprises sulphur hexafluoride or a perfluorinated low molecular weight hydrocarbon.

Please amend claim 6 as follows:

6. (once amended) [A]The method [as claimed in]of claim 5 wherein said perfluorinated hydrocarbon is perfluoropropane or perfluorobutane.

Please amend claim 7 as follows:

7. (once amended) [A]The method [as claimed in any of claims 4 to 6]of claim 4 wherein said gas is present as albumin-stabilised microbubbles.

Please amend claim 8 as follows:

8. (once amended) [A]The method [as claimed in any of claims 4 to 6]of claim 4 wherein said gas is present as phospholipid-stabilised microbubbles.

Please amend claim 9 as follows:

9. (once amended) [A]The method [as claimed in]of claim 8 wherein said phospholipid predominantly comprises phosphatidylserine.

Please amend claim 10 as follows:

10. (once amended) [A]The method [as claimed in any of claims 4 to 9]of claim 4 wherein the delivery vessel comprises a syringe positioned for upward delivery of said contrast agent.

Please amend claim 11 as follows:

11. (once amended) [A]The method [as claimed in any of the preceding claims]of claim 1 wherein said flushing medium is normal saline.

Please amend claim 12 as follows:

12. (once amended) [A]The method [as claimed in any of the preceding claims]of claim 1 wherein the admixed dispersion and flushing medium are administered by injection.

Please amend claim 13 as follows:

13. (once amended) [Apparatus]<u>An apparatus</u> for use in administration of a gravity segregating dispersion by continuous infusion, said apparatus comprising:

(i) a delivery device adapted to receive a dispersion-containing delivery vessel in an essentially vertical position and controllably to expel dispersion from an upper or lower extremity of said vessel;

(ii) mixing means adapted to effect admixture of said expelled dispersion with a flushing medium; and

(iii) conduit means adapted to conduct said admixed dispersion and flushing medium to an administration device.

Please amend claim 14 as follows:

14. (once amended) [Apparatus as claimed in]<u>The apparatus of</u> claim 13 wherein said delivery device is a syringe driver adapted to receive an essentially vertically positioned syringe.

Please amend claim 15 as follows:

15. (once amended) [Apparatus as claimed in claim 13 or claim 14]<u>The apparatus of claim 13</u> wherein said mixing means comprise a three way connector or tap

adapted to connect said delivery vessel and a source of flushing medium to said conduit means.

Please amend claim 16 as follows:

16. (once amended) [Apparatus as claimed in any of claims 13 to 15]The apparatus of claim 13 which further comprises flow rate controlling means for controlling the rate of flow of said flushing medium.

Please amend claim 17 as follows:

17. (once amended) [Apparatus as claimed in any of claims 13 to 16]The apparatus of claim 13 which further comprises means for inverting the position of said delivery vessel.

Remarks

Applicants have amended the specification to cross reference the parent application which is a PCT application designating the United States. Applicants have also amended the specification to add the required headings and move the text to be in the required order.

Applicants have cancelled claim 18, without prejudice. Applicants have amended claims 1-17 to more fully conform with U.S. practice. A version of the claims marked up

to show the amendments, as well as a clean version of the claims encompassing the amendments, is attached hereto.

Applicants are submitting herewith a copy of the International Search Report which issued on International Application number PCT/GB00/03310, of which the present application is a continuation. All of the publications cited in the International Search Report are listed on the attached Information Disclosure Statement.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Respectfully submitted,

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Claims (marked-up version showing amendments)

1. (once amended) [A]In a method of administering a gravity segregating dispersion to a subject by continuous infusion, [wherein said dispersion is controllably delivered]the improvement comprising controllably delivering said dispersion from an upper or lower extremity of an essentially vertically positioned delivery vessel and thereafter [is admixed]admixing with a flushing medium prior to administration to the subject.

2. (once amended) [A]The method [as claimed in]of claim 1 wherein said delivery vessel comprises a syringe.

3. (once amended) [A]The method [as claimed in]of claim 2 wherein delivery of said dispersion from said syringe is controlled by a syringe driver.

4. (once amended) [A]The method [as claimed in any of the preceding claims]of claim 1 wherein said dispersion is a gas-containing contrast agent.

5. (once amended) [A]The method [as claimed in]of claim 4 wherein said gas comprises sulphur hexafluoride or a perfluorinated low molecular weight hydrocarbon.

6. (once amended) [A]The method [as claimed in]of claim 5 wherein said perfluorinated hydrocarbon is perfluoropropane or perfluorobutane.

7. (once amended) [A]The method [as claimed in any of claims 4 to 6]of claim 4 wherein said gas is present as albumin-stabilised microbubbles.

8. (once amended) [A]The method [as claimed in any of claims 4 to 6]of claim 4 wherein said gas is present as phospholipid-stabilised microbubbles.

9. (once amended) [A]The method [as claimed in]of claim 8 wherein said phospholipid predominantly comprises phosphatidylserine.

10. (once amended) [A]The method [as claimed in any of claims 4 to 9]of claim 4 wherein the delivery vessel comprises a syringe positioned for upward delivery of said contrast agent.

11. (once amended) [A]The method [as claimed in any of the preceding claims]of claim 1 wherein said flushing medium is normal saline.

12. (once amended) [A]The method [as claimed in any of the preceding claims]of claim 1 wherein the admixed dispersion and flushing medium are administered by injection.

13. (once amended) [Apparatus]An apparatus for use in administration of a gravity segregating dispersion by continuous infusion, said apparatus comprising:

(i) a delivery device adapted to receive a dispersion-containing delivery vessel in an essentially vertical position and controllably to expel dispersion from an upper or lower extremity of said vessel;

(ii) mixing means adapted to effect admixture of said expelled dispersion with a flushing medium; and

(iii) conduit means adapted to conduct said admixed dispersion and flushing medium to an administration device.

14. (once amended) [Apparatus as claimed in]The apparatus of claim 13 wherein said delivery device is a syringe driver adapted to receive an essentially vertically positioned syringe.

15. (once amended) [Apparatus as claimed in claim 13 or claim 14]The apparatus of claim 13 wherein said mixing means comprise a three way connector or tap adapted to connect said delivery vessel and a source of flushing medium to said conduit means.

16. (once amended) [Apparatus as claimed in any of claims 13 to 15]The apparatus of claim 13 which further comprises flow rate controlling means for controlling the rate of flow of said flushing medium.

17. (once amended) [Apparatus as claimed in any of claims 13 to 16]The apparatus of claim 13 which further comprises means for inverting the position of said delivery vessel.

Claims (clean version encompassing amendments)

1. (once amended) In a method of administering a gravity segregating dispersion to a subject by continuous infusion, the improvement comprising controllably delivering said dispersion from an upper or lower extremity of an essentially vertically positioned delivery vessel and thereafter admixing with a flushing medium prior to administration to the subject.

2. (once amended) The method of claim 1 wherein said delivery vessel comprises a syringe.

3. (once amended) The method of claim 2 wherein delivery of said dispersion from said syringe is controlled by a syringe driver.

4. (once amended) The method of claim 1 wherein said dispersion is a gas-containing contrast agent.

5. (once amended) The method of claim 4 wherein said gas comprises sulphur hexafluoride or a perfluorinated low molecular weight hydrocarbon.

6. (once amended) The method of claim 5 wherein said perfluorinated hydrocarbon is perfluoropropane or perfluorobutane.

7. (once amended) The method of claim 4 wherein said gas is present as albumin-stabilised microbubbles.

8. (once amended) The method of claim 4 wherein said gas is present as phospholipid-stabilised microbubbles.

9. (once amended) The method of claim 8 wherein said phospholipid predominantly comprises phosphatidylserine.

10. (once amended) The method of claim 4 wherein the delivery vessel comprises a syringe positioned for upward delivery of said contrast agent.

11. (once amended) The method of claim 1 wherein said flushing medium is normal saline.

12. (once amended) The method of claim 1 wherein the admixed dispersion and flushing medium are administered by injection.

13. (once amended) An apparatus for use in administration of a gravity segregating dispersion by continuous infusion, said apparatus comprising:

(i) a delivery device adapted to receive a dispersion-containing delivery vessel in an essentially vertical position and controllably to expel dispersion from an upper or lower extremity of said vessel;

(ii) mixing means adapted to effect admixture of said expelled dispersion with a flushing medium; and

(iii) conduit means adapted to conduct said admixed dispersion and flushing medium to an administration device.

14. (once amended) The apparatus of claim 13 wherein said delivery device is a syringe driver adapted to receive an essentially vertically positioned syringe.

15. (once amended) The apparatus of claim 13 wherein said mixing means comprise a three way connector or tap adapted to connect said delivery vessel and a source of flushing medium to said conduit means.

16. (once amended) The apparatus of claim 13 which further comprises flow rate controlling means for controlling the rate of flow of said flushing medium.

17. (once amended) The apparatus of claim 13 which further comprises means for inverting the position of said delivery vessel.